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(54) Title: COMPONENT B AS CICATRIZANT

(57) Abstract

The present invention relates to the use of Component B as cicatrizant, in particular in the treatment of wounds, ulcers and other traumatic lesions to any of the tissues in the body.

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COMPONENT B AS CICATRIZANT

The present invention relates to the use of Component B as cicatrizant, in particular in the treatment of wounds, ulcers and other traumatic lesions to any of the tissues in the body.

Component B is a 81-amino acid protein originally isolated from human urine. The human gene has been cloned and expressed in CHO cells as recombinant human Component B. The molecule has a molecular weight of about 8.9 kD. It has been thoroughly described in WO 94/14259.

Such protein contains ten cysteines and bears a motif typical of serine protease enzymes. Sequence alignment to a protein data bank has shown some homologies of Component B with known molecules such as CD59, urokinase receptor (uPA-R) and some venom toxins.

Data obtained by the Applicant from the study of organ and tissue distribution in mice showed that eye, lung and skin are the sites in which Component B RNA is mainly expressed. In human tissues, Component B was found to be highly expressed in the squamous epithelia and mucosae, such as skin, oesophagus and exocervix, as determined by immunohistochemistry. Finally, EGF has been found to induce the expression of Component B RNA in human squamous epidermoid A431 cells.

Component B has been reported to have antiinflammatory, anticoagulant and antitumoral activity, as well as an activity as inihibitor of the binding of TGF-α to its receptor.

The Applicant has now found that Component B is also useful as cicatrizant, and it is, therefore, in particular, useful in the treatment of wounds, ulcers and other traumatic lesions to any of the tissues in the body.

Therefore, the main object of the present invention is the use of Component B for the manufacture of a pharmaceutical composition useful as cicatrizant, in particular in the treatment of wounds, ulcers and other traumatic lesions to any of the tissues in the body.

A further object of this invention is a method of treatment of wounds, ulcers and other traumatic lesions to any of the tissues in the body, comprising administering an effective amount of Component B, together with a pharmaceutically acceptable excipient.

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Another object of the invention are pharmaceutical compositions prepared as described above.

For the methods of preparation of Component B and for its amino acid sequence, reference is made to the disclosure of WO 94/14259.

The administration of the active ingredient may be by oral, intravenous, intramuscular, subcutaneous or topical route. Other routes of administration, which may establish the desired blood levels of the respective ingredients, are comprised by the present invention.

For the human therapy the preferred doses are 1 mg/kg or less for the systemic administration and 4 $\mu g/cm^2$ or less for the topical administration.

The invention will now be described by means of the following Examples, which should not be construed as in any way limiting the present invention. The Examples will refer to the Figures as specified here below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: the effect of the intravenous administration of Component B in comparison with that of betametasone (Bentelan®) on the experimental wound healing is shown. In particular, the results of Experiment 1 are summarised. Test drugs were administered daily for 6 consecutive days from day 0 (the day of wound induction) through 5.

Figure 2: the effect of the intravenous administration of Component B (batch 004-001b) in comparison with that of betametasone (Bentelan®) on the experimental wound healing is shown. In particular, the results of Experiment 2 are summarised. Test drugs were administered daily for 6 consecutive days from day 0 (the day of wound induction) through 5.

Figure 3: the effect of the topical application of Component B (batch 004-001) on the experimental wound healing is shown. In particular, the results of Experiment 3 are summarised. Test drugs were topically applied for 5 consecutive days from day 0 (the day of wound induction) through 4.

Figure 4: the effect of the topical application of bovine serum albumin on the experimental wound healing is shown. In particular, the results of Experiment 4 are

summarised. Test drugs were topically applied for 5 consecutive days from day 0 (the day of wound induction) through 4.

Figure 5: the sigmoidal dose response analysis applied to the results of Experiment 1 is reported. The effect of the intravenous administration of Component B (batches 004-001 and 004-001b, indicated as "001" and "001b", respectively) and betametasone (Bentelan ®) on the experimental wound healing is, therefore, statistically evaluated on the basis of the results of Experiment 1.

Figure 6: the sigmoidal dose response analysis applied to the results of Experiment 2 is reported. The effect of the intravenous administration of Component B (batch 004-001b, indicated as "001b") and betametasone (Bentelan®) on the experimental wound healing is, therefore, statistically evaluated on the basis of the results of Experiment 2.

Figure 7: the sigmoidal dose response analysis applied to the cumulated results of Experiments 1 and 2 is reported. The effect of the intravenous administration of Component B (batch 004-001b) on the experimental wound healing is, therefore, statistically evaluated on the basis of the combination of the results of Experiments 1 and 2.

Figure 8: the sigmoidal dose response analysis applied to the cumulative frequency, relative to combination of Experiments 1 and 2 is reported. The effect of Component B (batch 004-001b) is so evaluated.

Figure 9: the sigmoidal dose response analysis applied to the results of Experiment 3 is reported. The effect of the topical and intravenous administration of Component B (batch 004-001) on the experimental wound healing is, therefore, statistically evaluated on the basis of the results of Experiment 3.

Figure 10: : the sigmoidal dose response analysis applied to the results of Experiment 4 is reported. A comparison of the effect between buffer and BSA in wound reduction is, therefore, statistically evaluated on the basis of the results of Experiment 4.

EXAMPLES

Materials

Animals

SPF CD-1 mice of both sexes, purchased from Charles River Italia (Calco, Como, Italy), were used for the experiments after an acclimatisation period of at least

BNSDOCID: <WO___9739765A1_I_>

seven days under controlled environmental conditions (temperature: 22±2°C; humidity: 55±10% and a light/dark cycle of 12 hours).

Test compounds

- rec-hComponent B batch 004-001 (sulphated form) and 004-001b (non-sulphated form) expressed in CHO cells and produced essentially as described in WO 94/14259.
- Commercial preparation of betametasone (Bentelan®) from Glaxo (Verona, Italy).
- Sodium chloride 0.9 % (saline), from Baxter (Trieste, Italy).
- Bovine serum albumin (BSA), fraction V, supplied by Sigma Chemical Co. (St. Louis MO, USA).

Methods

Experimental full-thickness wound healing

The method used was that suggested by J.J.P. Morton and M.H. Malone (Morton J.J.P. and Malone M.H., Arch. Int. Pharmacodyn. 196:117, 1972), who used this procedure for the evaluation of a number of drugs for their vulnerary activity in rats.

For the present study of Component B, the original method was suitably modified to be used in mice, as follows.

A circular ink mark (1 cm diameter) was impressed on the dorsal region of male mice (30-35 g, 6-7 week-old), and the skin of this marked area (including *panniculus carnosus* and adherent tissues) was excised using surgical scissors and forceps. The wound was then blotted dry with gauze pads until haemostasis occurred. On day 0, i. e. the day of surgery, longitudinal, transverse and two diagonal measurements (relative to the vertebral column) were made of the diameter of the wound to the nearest 0.1 mm using a direct reading caliper. The exact points of measurements were preserved by marking the adjacent skin with indelible ink. Subsequent wound measurements were made every other day except on Sunday up to complete wound closure. Both surgery and measurements were made under light ether anaesthesia of the mice.

The area of each wound was obtained by multiplying the square of its mean diameter by 0.7854. Per cent wound closure was then calculated relative to day 0. The mean per cent wound closure values for each measurement day were tabulated for each experimental group and the closure time 50% (CT_{50}) interpolated.

Systemic treatment

Two experiments (Experiments 1 and 2) were performed. In the second experiment, on each measurement day, the measurements were performed by the same operator who was unaware of the treatment schedules. In each experiment the animals were divided into 4 groups and treated according to the following schedule.

Group number	1st experiment	2nd experiment
1	Saline 10 ml/kg, i.p.	Saline 10 ml/kg, i.v.
2	Component B 004-001, 1 mg/kg, i.v.	Component B 004-001b, 0.1 mg/kg, i.v.
3	Component B 004-001b, 1 mg/kg, i.v.	Component B 004-001b, 1 mg/kg, i.v.
4	Betametasone, 1 mg/kg, i.p.	Betametasone, 1 mg/kg, i.v.

The animals were treated once a day for 6 consecutive days. The body weight of the animals was monitored for the whole duration of the study.

Topical treatment

In a further experiment (Experiment 3) the effect of the topical application of different doses of Component B (batch 004-001) were studied by using the already described procedure for wound induction following the treatment schedule reported in the table herebelow.

Group number	Treatment
1	Phosphate buffer 0.05 ml, topically
2	Component B 004-001, 1 µg, topically
3	Component B 004-001, 2 µg, topically
4	Component B 004-001, 4 µg, topically
5	Component B 1 mg/kg, i.v.

The solutions of the test product were applied (volume 0.05 ml) onto the wounds on days 1 and 2, whereas in the successive days, when the scab had been formed, they were injected underneath the scab by a syringe equipped with a 25G needle.

Component B administered i.v. at the dose of 1 mg/kg, has been used as positive reference standard.

To rule out the possibility of aspecific effects of topical application of a proteic solution, in a parallel experiment the effect of BSA, at the same molar concentrations (8.8×10^{-6}M) as Component B, was assayed topically in comparison to phosphate buffer (Experiment 4).

Results

Wound healing

Figure 1 reports the data of the first Experiment, in which the activity of two batches (004-001 and 004-001b) of Component B were compared. Both of them were capable of accelerating the cicatrization process, their effects being already evident after 1 day of treatment. CT_{50}, i.e. the time when 50% wound reduction occurs, is 3.0 and 3.4 days, respectively, these values being not statistically different. By contrast, CT_{50}'s of 7.8 and 7.2 days were observed with betametasone (Bentelan®) and saline, respectively (see the paragraph entitled "Statistical Analysis").

In the second Experiment (Figure 2) two doses of Component B (batch 004-001b) were studied. At the highest dose, 1 mg/kg, the CT_{50} was 3.7 days whereas it was of 6.6 days at the lowest dose (0.1 mg/kg). The saline and betametasone treated groups displayed CT_{50}'s of 9.1 and 10 days, respectively (see the paragraph entitled "Statistical Analysis").

The positive effect of Component B on wound healing was also confirmed by another index, namely ET_{50}, indicating the time when 50% of the animals showed complete wound closure (see the paragraph entitled "Statistical Analysis").

The results of the experiment where Component B (batch 004-001) was applied topically onto the wound (Experiment 3), are reported in Figure 3. The compound was studied at doses of 1, 2 and 4 μg/day for 5 consecutive days. All doses assayed were capable of enhancing the wound healing process as compared to controls. In particular,

doses of 2 and 4 μg provided CT_{50} values of 3.8 and 4.4, respectively, which are comparable to that found (3.9) with 1 mg/kg of Component B given i.v. With the lowest dose (1 μg), a CT_{50} value of 5.3 days was observed, which is higher than those obtained with the other two topical doses, but still significantly different from controls (see the paragraph entitled "Statistical Analysis").

These data suggest that a dose of 2 μg, topically applied on the wound, produces the maximal effect and that 1 μg is still effective in enhancing the cicatrization process.

In order to verify whether the positive effect of Component B on the wound healing process is a specific characteristic of the product, a parallel experiment was carried out, in which the effect of BSA, at the same molar concentration of Component B, was compared to that of phosphate buffer (Experiment 4). These data are reported in Figure 4. CT_{50}'s of 9.9 and 7.9 days were recorded with BSA and phosphate buffer, respectively. The above values are not significantly different (see the paragraph entitled "Statistical Analysis"), thus indicating that a standard protein solution, like BSA, does not influence the cutaneous wound repair.

The individual data of these experiments are reported in Tables 1A-4B.

Statistical Analysis

Statistical strategy:

The statistical analysis was aimed at comparing the effect over the time of two preparations of Component B (Comp. B) both *vs* saline and the reference drug Bentelan.

Furthermore, the effects of the systemic and the topical administration of one preparation of Component B have been also evaluated.

In accordance with the treatment protocol the effect of the test drugs was studied considering the entire observation period.

The wound reduction experiment was repeated twice in order to confirm the Comp B effect at different dose levels.

Statistical test

The Sigmoidal Dose Response Analysis for the evaluation of the CT_{50} (i.e. the time when the wound area is reduced by 50%) was used as the statistical test (see Finney D. J., Biometrics, 32, pp. 721-40, 1976).

Statistical units

1) Wound reduction (CT_{50}): Average percentage of variation vs average basal values.

2) Cumulative Frequency (ET_{50}) : Cumulative frequency of animals showing a complete wound closure at each time point.

Groups of treatment (Exp. No 1)

1 - Saline - 10 ml/kg/day, i.p. for 6 days

2 - Bentelan - 1 mg/kg/day, i.p. for 6 days

3 - CompB 004-001- 1 mg/kg/day, i.v. for 6 days

4 - CompB 004-001b- 1 mg/kg/day, i.v. for 6 days

Groups of treatment (Exp. No 2)

1 - Saline - 10 ml/kg/day, i.v. for 6 days

2 - Bentelan - 1 mg/kg/day, i.v. for 6 days

3 - CompB 004-001b- 0.1 mg/kg/day, i.v. for 6 days

4 - CompB 004-001b- 1 mg/kg/day, i.v. for 6 days

Groups of treatment (Exp. No 3)

1 - Phosphate buffer- 50 µl/day, topical for 5 days

3 - CompB 004-001- 1 µg/day, topical for 5 days

3 - CompB 004-001- 2 µg/day, topical for 5 days

4 - CompB 004-001- 4 µg/day, topical for 5 days

5 - CompB 004-001- 1 mg/kg/day, i.v. for 5 days

Groups of treatment (Exp. No 4)

1 -Phosphate buffer - 50 µl/day, topical for 5 days

2 -Bovine serum albumin (BSA) - 50 µl/day (8.8×10^{-6}M), topical for 5 days

Treatment schedule (for Experiments 1, 2, 3 and 4)

Phase 1: Repeated treatment days according to the above treatment-group description.

Phase 2: Observation period up to the day of complete wound closure.

Results of the statistical analysis

The diagrams (sigmoidal dose response analysis) reported in Figures 5-10 summarise the effect of the test drugs using as the variable the wound area.

Experiment. 1

Reference is made to Figure 5.

The results of the sigmoidal dose response analysis (CT_{50}) applied to the wound area, relative to experiment 1, are reported in the following table.

Test Drug	CT_{50} (days)	Confidence Limits	R^2
Saline	7.2	6.2 - 8.3	0.96
Bentelan 1 mg/kg	7.8	6.9 - 8.8	0.97
CompB 004-001 1 mg/kg	3.0	2.5 - 3.7	0.97
CompB 004-001b 1 mg/kg	3.4	2.8 - 4.1	0.97

Experiment 2

Reference is made to Figure 6.

The results of the sigmoidal dose response analysis (CT_{50}) applied to the wound area, relative to experiment 2 are reported in the following table.

Test Drug	CT_{50} (days)	Confidence Limits	R^2
Saline	9.1	8.4 - 9.9	0.98
Bentelan 1 mg/kg	10.0	9.6 - 10.4	0.99
CompB 004-001b 0.1 mg/kg	6.6	5.5 - 7.7	0.94
CompB 004-001b 1 mg/kg	3.7	2.8 - 4.8	0.92

Combination of Experiments 1 and 2

Reference is made to Figure 7.

The results obtained from the combination of the data of treatment groups common to both experiments 1 and 2, i.e. saline vs CompB-004-001b 1 mg/kg are summarised.

BNSDOCID: <WO___9739765A1_I_>

In addition, the frequency over the time of the animals showing complete closure of the wound was also evaluated (by Sigmoidal Dose-Response Analysis) from the cumulated data of Experiments 1 and 2.

The results of the sigmoidal dose response analysis (CT_{50}) applied to the wound area, relative to the combination of experiments 1 and 2, are reported in the following table.

Test Drug	CT_{50} (days)	Confidence Limits	R^2
Saline	8.2	7.5 - 8.9	0.95
CompB 004-001b 1 mg/kg	3.5	3.0 - 4.1	0.95

For the cumulative frequency, reference is made to Figure 8.

The results of the sigmoidal dose response analysis (ET_{50}) applied to the cumulative frequency, relative to the combination of experiments 1 and 2, are reported in the following table.

Test Drug	ET_{50} (days)	Confidence Limits	R^2
Saline	16.1	15.4 - 16.9	0.98
CompB 004-001b 1 mg/kg	11.7	11.2 - 12.1	0.99

In conclusion, the comparison among CT_{50} values and among ET_{50} values is a good estimate of the effect of each test drug on the experimental model.

Both CompB-001 (1 mg/kg, i.v.) and CompB-001b (dose levels 0.1 mg/kg and 1 mg/kg, i.v.) were found to be statistically different from saline and Bentelan in Experiments 1 and 2. The results of the combination of treatment groups common to Experiments 1 and 2 confirm the effect of the i.v. route of administration with CompB 1 mg/kg.

Experiment 3

Reference is made to Figure 9.

A further set of experiments was performed in which the product was topically applied. The intravenous route was used as positive reference standard. The data were analysed using the same statistical models as above.

The results of the sigmoidal dose response analysis (CT_{50}) applied to the wound area, relative to experiment 3, are reported in the following table.

Test Drug	CT_{50} (days)	Confidence Limits	R^2
Phosphate Buffer	8.3	7.3 - 9.5	0.96
CompB-001 1 mcg topical	5.3	4.1 - 6.9	0.91
CompB-001 2 mcg topical	3.8	2.9 - 4.9	0.92
CompB-001 4 mcg topical	4.4	3.4 - 5.6	0.92
CompB-001 1 mg/kg i.v.	3.9	3.0 - 5.2	0.92

In conclusion, topical administration of CompB-001b showed, at all doses tested, a wound reduction (CT_{50}) significantly different from phosphate buffer.

Experiment 4

Reference is made to Figure 10.

The diagram reports the comparison between topical application of phosphate buffer and BSA in wound reduction in order to rule out possible aspecific effects of Component B.

The results of the sigmoidal dose response analysis (CT_{50}) applied to the wound area, relative to Experiment 4, are reported in the following table.

Test Drug	CT_{50} (days)	Confidence Limits	R^2
Buffer	7.9	7.2 - 8.7	0.98
BSA	9.9	8.5 - 11.4	0.95

The above results did not show any differences between the topical application of phosphate buffer and BSA.

BNSDOCID: <WO___9739765A1_I_>

Conclusions of all the study

The interesting result of this study is the activity of Component B in the cicatrization process both when administered intravenously or by topical application. The experimental model used in this study is directly related to the human trauma counterpart and is predictive for the application of Component B in the healing of traumatic lesions of the skin and in plastic and reconstructive surgery of mucosae and epithelia.

Table 1A: Wound healing data - Experiment 1

Comp B 004-001 : 1 mg/kg, i.v.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.622	0.529	-14.9518	0.318	-48.8746	0.135	-78.2958	0.06	-90.3537
0.813	0.745	-8.36408	0.566	-30.3813	0.604	-25.7073	0.483	-40.5904
0.761	0.701	-7.88436	0.341	-55.1905	0.201	-73.5874	0.111	-85.4139
0.644	0.418	-35.0932	0.289	-55.1242	0.125	-80.5901	0.103	-84.0062
0.825	0.549	-33.4545	0.266	-67.7576	0.133	-83.8788	0.049	-94.0606
0.724	0.624	-13.8122	0.432	-40.3315	0.313	-56.768	0.251	-65.3315
0.679	0.697	2.650957	0.402	-40.7953	0.214	-68.4831	0.114	-83.2106
0.769	0.478	-37.8414	0.412	-46.4239	0.3	-60.9883	0.137	-82.1847
0.709	0.48	-32.299	0.374	-47.2496	0.285	-59.8025	0.195	-72.4965
Mean ± S.D.								
0.727	0.580	-20.117	0.378	-48.014	0.257	-65.345	0.167	-77.516
0.071	0.116	14.736	0.090	10.711	0.150	17.734	0.134	16.334

Day 9		Day 11		Day 14				
area	% variat.	area	% variat.	area	% variat.			
0.039	-93.7299	0.031	-95.0161	0	-100			
0.288	-64.5756	0.104	-87.2079	0.039	-95.203			
0.06	-92.1156	0.009	-98.8173	0	-100			
0.046	-92.8571	0	-100	0	-100			
0.043	-94.7879	0	-100	0	-100			
0.173	-76.105	0	-100	0	-100			
0.084	-87.6289	0.104	-84.6834	0.13	-80.8542			
0.1	-86.9961	0.06	-92.1977	0	-100			
0.196	-72.3554	0	-100	0	-100			
Mean ± S.D.								
0.114	-84.572	0.034	-95.325	0.019	-97.340			
0.086	10.896	0.044	6.007	0.044	6.382			

Day 16		Day 18						
area	% variat.	area	% variat.					
0	-100	0	-100					
0.007	-99.139	0	-100					
0	-100	0	-100					
0	-100	0	-100					
0	-100	0	-100					
0	-100	0	-100					
0.046	-93.2253	0	-100					
0	-100	0	-100					
0	-100	0	-100					
Mean ± S.D.								
0.006	-99.152	0	-100.000					
0.015	2.241	0.000	0.000					

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Table 1B: Wound healing data - Experiment 1

Comp B 004-001b : 1 mg/kg, i.v.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.535	0.505	-5.60748	0.402	-24.8598	0.273	-48.972	0.162	-69.7196
0.656	0.611	-6.85976	0.194	-70.4268	0.083	-87.3476	0.017	-97.4085
0.647	0.631	-2.47295	0.365	-43.5858	0.3	-53.6321	0.114	-82.3802
0.813	0.508	-37.5154	0.363	-55.3506	0.177	-78.2288	0.142	-82.5338
0.781	0.622	-20.3585	0.385	-50.7042	0.289	-62.9962	0.169	-78.3611
0.785	0.656	-16.4331	0.435	-44.586	0.334	-57.4522	0.205	-73.8854
0.777	0.559	-28.0566	0.397	-48.906	0.361	-53.5393	0.259	-66.6667
0.724	0.618	-14.6409	0.528	-27.0718	0.455	-37.1547	0.323	-55.3867
0.747	0.756	1.204819	0.36	-51.8072	0.244	-67.336	0.256	-65.7296
0.903	0.729	-19.2691	0.561	-37.8738	0.27	-70.0997	0.175	-80.6202
Mean ± S.D.								
0.737	0.620	-15.001	0.399	-45.517	0.279	-61.676	0.182	-75.269
0.103	0.083	12.021	0.100	13.438	0.101	14.717	0.086	11.665

Day 9		Day 11		Day 14	
area	% variat.	area	% variat.	area	% variat.
0.109	-79.6262	0.075	-85.9813	0.073	-86.3551
0	-100	0	-100	0	-100
0.057	-91.1901	0.054	-91.6538	0	-100
0.11	-86.4699	0	-100	0	-100
0.069	-91.1652	0.046	-94.1101	0	-100
0.146	-81.4013	0.008	-98.9809	0	-100
0.179	-76.9627	0.026	-96.6538	0	-100
0.235	-67.5414	0.017	-97.6519	0	-100
0.196	-73.7617	0	-100	0	-100
0.077	-91.4729	0.049	-94.5736	0	-100
Mean ± S.D.					
0.118	-83.959	0.028	-95.961	0.007	-98.636
0.072	9.844	0.027	4.533	0.023	4.315

Day 16		Day 18	
area	% variat.	area	% variat.
0.028	-94.7664	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
Mean ± S.D.			
0.003	-99.477	0	-100.000
0.009	1.655	0.000	0.000

Table 1C: Wound healing data - Experiment 1

Bentelan 1mg/kg, i.p.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.671	0.634	-5.51416	0.64	-4.61997	0.507	-24.4411	0.265	-60.5067
0.76	0.737	-3.02632	0.667	-12.2368	0.535	-29.6053	0.445	-41.4474
0.703	0.737	4.836415	0.618	-12.091	0.277	-60.5974	0.246	-65.0071
0.885	0.898	1.468927	0.697	-21.2429	0.735	-16.9492	0.759	-14.2373
0.788	0.762	-3.29949	0.799	1.395939	0.594	-24.6193	0.626	-20.5584
0.701	0.662	-5.56348	0.705	0.570613	0.493	-29.6719	0.46	-34.3795
0.654	0.631	-3.51682	0.666	1.834862	0.466	-28.7462	0.491	-24.9235
Mean ± S.D.								
0.737	0.723	-2.088	0.685	-6.627	0.515	-30.661	0.470	-37.294
0.080	0.094	3.847	0.059	8.820	0.138	13.935	0.183	19.567

Day 9		Day 11		Day 14		
area	% variat.	area	% variat.	area	% variat.	
0.201	-70.0447	0.199	-70.3428	0.056	-91.6542	
0.352	-53.6842	0.339	-55.3947	0.091	-88.0263	
0.215	-69.4168	0.084	-88.0512	0	-100	
0.551	-37.7401	0.331	-62.5989	0.176	-80.113	
0.535	-32.1066	0.275	-65.1015	0	-100	
0.302	-56.9187	0.162	-76.8902	0	-100	
0.263	-59.7859	0.173	-73.5474	0.031	-95.2599	
Mean ± S.D.						
0.346	-54.242	0.223	-70.275	0.051	-93.579	
0.144	14.609	0.095	10.627	0.065	7.554	

Day 16		Day 18		
area	% variat.	area	% variat.	
0.011	-98.3607	0	-100	
0.008	-98.9474	0	-100	
0	-100	0	-100	
0.031	-96.4972	0	-100	
0	-100	0	-100	
0	-100	0	-100	
0.031	-95.2599	0	-100	
Mean ± S.D.				
0.012	-98.438	0.000	-100.000	
0.014	1.891	0.000	0.000	

BNSDOCID: <WO___9739765A1_I_>

Table 1D: Wound healing data - Experiment 1

Saline 10 ml/kg, i.p.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.937	0.929	-0.854	0.636	-32.1238	0.398	-57.524	0.275	-70.651
0.997	0.948	-4.915	0.675	-32.2969	0.601	-39.7192	0.463	-53.5607
0.833	0.856	2.761	0.854	2.521008	0.793	-4.80192	0.749	-10.084
0.804	0.796	-0.995	0.797	-0.87065	0.767	-4.60199	0.751	-6.59204
0.697	0.825	18.364	0.605	-13.1994	0.644	-7.60402	0.64	-8.17791
0.729	0.745	2.195	0.626	-14.1289	0.454	-37.7229	0.385	-47.1879
0.618	0.645	4.369	0.518	-16.1812	0.327	-47.0874	0.209	-66.1812
0.72	0.594	-17.500	0.528	-26.6667	0.287	-60.1389	0.189	-73.75
Mean ± S.D.								
0.792	0.792	0.428	0.655	-16.618	0.534	-32.400	0.458	-42.023
0.127	0.126	9.996	0.119	13.199	0.195	23.444	0.232	29.254

Day 9		Day 11		Day 14	
area	% variat.	area	% variat.	area	% variat.
0.127	-86.4461	0.139	-85.1654	0	-100
0.366	-63.2899	0.297	-70.2106	0.039	-96.0883
0.608	-27.0108	0.339	-59.3037	0.151	-81.8727
0.541	-32.7114	0.36	-55.2239	0.1	-87.5622
0.512	-26.5423	0.347	-50.2152	0.128	-81.6356
0.331	-54.5953	0.238	-67.3525	0.012	-98.3539
0.132	-78.6408	0	-100	0	-100
0.085	-88.1944	0	-100	0	-100
Mean ± S.D.					
0.338	-57.179	0.215	-73.434	0.054	-93.189
0.206	26.106	0.151	19.519	0.063	8.172

Day 16		Day 18	
area	% variat.	area	% variat.
0	-100	0	-100
0	-100	0	-100
0.02	-97.599	0	-100
0	-100	0	-100
0.026	-96.2697	0	-100
0	-100	0	-100
0	-100	0	-100
0	-100	0	-100
Mean ± S.D.			
0.006	-99.234	0.000	-100.000
0.011	1.463	0.000	0.000

Table 2A: Wound healing data - Experiment 2

Comp B 004-001b: 0.1 mg/kg, i.v.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.679	0.58	-14.5803	0.561	-17.3785	0.566	-16.6421	0.347	-48.8954
0.693	0.677	-2.3088	0.635	-8.36941	0.603	-12.987	0.493	-28.86
1.002	0.759	-24.2515	0.84	-16.1677	0.749	-25.2495	0.525	-47.6048
0.833	0.677	-18.7275	0.701	-15.8463	0.584	-29.892	0.401	-51.8607
0.671	0.597	-11.0283	0.458	-31.7437	0.412	-38.5991	0.282	-57.9732
0.651	0.526	-19.2012	0.604	-7.21966	0.556	-14.5929	0.424	-34.8694
0.682	0.755	10.70381	0.452	-33.7243	0.512	-24.9267	0.242	-64.5161
0.817	0.601	-26.4382	0.55	-32.6805	0.486	-40.5141	0.408	-50.0612
0.693	0.538	-22.3665	0.418	-39.6825	0.307	-55.6999	0.246	-64.5022
0.799	0.58	-27.4093	0.58	-27.4093	0.461	-42.3029	0.418	-47.6846
0.777	0.686	-11.7117	0.563	-27.5418	0.433	-44.2728	0.282	-63.7066
Mean ± S.D.								
0.754	0.634	-15.211	0.578	-23.433	0.515	-31.425	0.379	-49.683
0.105	0.081	11.420	0.120	10.927	0.117	13.897	0.098	11.427

Day 9		Day 11		Day 14		Day 16	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.347	-48.8954	0.196	-71.134	0.009	-98.6745	0	-100
0.309	-55.4113	0.139	-79.9423	0.039	-94.3723	0.012	-98.27
0.454	-54.6906	0.146	-85.4291	0.058	-94.2116	0.018	-98.20
0.206	-75.2701	0.053	-93.6375	0	-100	0	-100
0.238	-64.5306	0.142	-78.8376	0.04	-94.0387	0	-100
0.329	-49.4624	0.216	-66.8203	0.15	-76.9585	0.052	-92.01
0.179	-73.7537	0.046	-93.2551	0	-100	0	-100
0.282	-65.4835	0.177	-78.3354	0	-100	0	-100
0.231	-66.6667	0.122	-82.3954	0	-100	0	-100
0.409	-48.811	0.203	-74.5932	0	-100	0	-100
0.225	-71.0425	0.105	-86.4865	0.008	-98.9704	0	-100
Mean ± S.D.							
0.292	-61.274	0.140	-80.988	0.027636	-96.111	0.007	-98.953
0.087	10.150	0.057	8.449	0.046	6.842	0.016	2.408

Table 2Acont.: Wound healing data -Experiment 2

Comp B 004-001b: 0.1 mg/kg, i.v.						
Day 18		Day 21		Day 23		
area	% variat.	area	% variat.	area	% variat.	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
Mean ± S.D.						
0	-100.000	0	-100.000	0	-100.000	
0.000	0.000	0.000	0.000	0.000	0.000	

Table 2B: Wound healing data - Experiment 2

Comp B 004-001b: 1 mg/kg, i.v.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.769	0.601	-21.8466	0.455	-40.8322	0.297	-61.3784	0.121	-84.2653
0.763	0.525	-31.1927	0.493	-35.3866	0.464	-39.1874	0.451	-40.8912
0.964	0.712	-26.1411	0.358	-62.8631	0.287	-70.2282	0.134	-86.0996
0.712	0.573	-19.5225	0.421	-40.8708	0.563	-20.927	0.179	-74.8596
0.763	0.59	-22.6737	0.266	-65.1376	0.155	-79.6855	0.054	-92.9227
0.793	0.747	-5.80076	0.415	-47.6671	0.334	-57.8815	0.185	-76.6709
0.785	0.451	-42.5478	0.238	-69.6815	0.199	-74.6497	0.168	-78.5987
0.747	0.701	-6.15797	0.458	-38.6881	0.398	-46.7202	0.29	-61.178
0.873	0.765	-12.3711	0.73	-16.3803	0.667	-23.5968	0.515	-41.008
0.979	0.867	-11.4402	0.667	-31.8693	0.594	-39.3258	0.448	-54.239
0.833	0.716	-14.0456	0.594	-28.6915	0.528	-36.6146	0.395	-52.581
1.225	0.72	-41.2245	0.528	-56.898	0.458	-62.6122	0.384	-68.6531
Mean ± S.D.								
0.8505	0.664	-21.247	0.469	-44.581	0.412	-51.067	0.277	-67.664
0.145	0.117	12.337	0.148	16.249	0.161	19.536	0.156	17.540

Day 9		*Day 11*		*Day 14*		*Day 16*		
area	*% variat.*	*area*	*% variat.*	*area*	*% variat.*	*area*	*% variat.*	
0.056	-92.7178	0.044	-94.2783	0	-100	0	-100	
0.344	-54.9148	0.146	-80.865	0	-100	0	-100	
0.03	-96.888	0	-100	0	-100	0	-100	
0.171	-75.9831	0.021	-97.0506	0	-100	0	-100	
0.038	-95.0197	0	-100	0	-100	0	-100	
0.061	-92.3077	0.024	-96.9735	0	-100	0	-100	
0.039	-95.0318	0	-100	0	-100	0	-100	
0.138	-81.5261	0.038	-94.913	0	-100	0	-100	
0.344	-60.5956	0.192	-78.0069	0	-100	0	-100	
0.186	-81.001	0.019	-98.0592	0	-100	0	-100	
0.238	-71.4286	0.159	-80.9124	0	-100	0	-100	
0.392	-68	0.148	-87.9184	0	-100	0	-100	
Mean ± S.D.								
0.170	-80.451	0.066	-92.415	0	-100.000	0	-100.000	
0.133	14.429	0.073	8.257	0.000	0.000	0.000	0.000	

BNSDOCID: <WO___9739765A1_I_>

Table 2C: Wound healing data - Experiment 2

Bentelan 1 mg/kg, i.v.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.789	0.813	3.041825	0.767	-2.78834	0.615	-22.0532	0.565	-28.3904
0.769	0.831	8.062419	0.846	10.013	0.833	8.322497	0.751	-2.3407
0.805	0.741	-7.95031	0.751	-6.70807	0.763	-5.21739	0.525	-34.7826
0.751	0.86	14.51398	0.825	9.853529	0.997	32.75632	0.586	-21.9707
0.842	0.864	2.612827	0.858	1.900238	0.773	-8.19477	0.675	-19.8337
0.856	0.739	-13.6682	0.769	-10.1636	0.712	-16.8224	0.636	-25.7009
0.651	0.679	4.301075	0.69	5.990783	0.626	-3.84025	0.555	-14.7465
0.769	0.679	-11.7035	0.636	-17.2952	0.656	-14.6944	0.622	-19.1157
0.763	0.86	12.71298	0.869	13.89253	0.777	1.834862	0.751	-1.57274
0.675	0.679	0.592593	0.769	13.92593	0.709	5.037037	0.655	-2.96296
0.805	0.667	-17.1429	0.69	-14.2857	0.72	-10.559	0.622	-22.7329
0.644	0.886	37.57764	0.809	25.62112	0.565	-12.2671	0.551	-14.441
Mean ± S.D.								
0.760	0.775	2.746	0.773	2.496	0.729	-3.808	0.625	-17.383
0.070	0.086	14.999	0.073	13.020	0.115	14.627	0.074	10.667

Day 9		Day 11		Day 14		Day 16		
area	% variat.	area	% variat.	area	% variat.	area	% variat.	
0.317	-59.8226	0.258	-67.3004	0.151	-80.8619	0.081	-89.7338	
0.424	-44.8635	0.344	-55.2666	0.222	-71.1313	0.11	-85.6957	
0.457	-43.2298	0.312	-61.2422	0.181	-77.5155	0.066	-91.8012	
0.755	0.532623	0.587	-21.8375	0.369	-50.8655	0.216	-71.2383	
0.545	-35.2732	0.315	-62.5891	0.117	-86.1045	0.026	-96.9121	
0.43	-49.7664	0.259	-69.743	0.118	-86.215	0.035	-95.9112	
0.396	-39.1705	0.24	-63.1336	0.071	-89.0937	0	-100	
0.433	-43.6931	0.309	-59.8179	0.212	-72.4317	0.025	-96.749	
0.594	-22.1494	0.433	-43.2503	0.092	-87.9423	0.016	-97.903	
0.415	-38.5185	0.325	-51.8519	0.203	-69.9259	0.036	-94.6667	
0.499	-38.0124	0.302	-62.4845	0.157	-80.4969	0.013	-98.3851	
0.312	-51.5528	0.124	-80.7453	0.033	-94.8758	0	-100	
Mean ± S.D.								
0.465	-38.793	0.317	-58.272	0.161	-78.955	0.052	-93.250	
0.122	15.500	0.112	14.749	0.088	11.768	0.061	8.146	

Table 2Ccont.: Wound healing data - Experiment 2

Bentelan 1 mg/kg, i.v.						
Day 18		*Day 21*		*Day 23*		
area	*% variat.*	*area*	*% variat.*	*area*	*% variat.*	
0.02	-97.4651	0	-100	0	-100	
0.059	-92.3277	0.047	-99.417	0	-100	
0.01	-98.7578	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0.015	-98.0494	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
Mean ± S.D.						
0.009	-98.883	0.004	-99.951	0.000	-100.000	
0.017	2.250	0.014	0.168	0.000	0.000	

BNSDOCID: <WO___9739765A1_I_>

Table 2D: Wound healing data - Experiment 2

Saline 10 ml/kg, i.v.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.58	0.594	2.413793	0.535	-7.75862	0.538	-7.24138	0.466	-19.6552
0.773	0.755	-2.32859	0.763	-1.29366	0.584	-24.4502	0.561	-27.4256
0.735	0.785	6.802721	0.779	5.986395	0.735	0	0.622	-15.3741
0.805	0.666	-17.2671	0.655	-18.6335	0.615	-23.6025	0.385	-52.1739
0.701	0.629	-10.271	0.629	-10.271	0.546	-22.1113	0.493	-29.6719
0.686	0.671	-2.18659	0.584	-14.8688	0.535	-22.0117	0.478	-30.3207
0.601	0.59	-1.83028	0.58	-3.49418	0.536	-10.8153	0.451	-24.9584
0.759	0.747	-1.58103	0.72	-5.13834	0.627	-17.3913	0.551	-27.4045
Mean ± S.D.								
0.705	0.680	-3.281	0.656	-6.934	0.590	-15.953	0.501	-28.373
0.080	0.075	7.423	0.090	7.796	0.069	8.978	0.074	10.892

Day 9		Day 11		Day 14		Day 16	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.325	-43.9655	0.206	-64.4828	0.206	-64.4828	0.104	-82.069
0.339	-56.1449	0.238	-69.2109	0.181	-76.5847	0.116	-84.9935
0.436	-40.6803	0.187	-74.5578	0.197	-73.1973	0.067	-90.8844
0.408	-49.3168	0.28	-65.2174	0.216	-73.1677	0.047	-94.1615
0.369	-47.3609	0.249	-64.4793	0.238	-66.0485	0.036	-94.8645
0.246	-64.1399	0.273	-60.2041	0.175	-74.4898	0	-100
0.282	-53.0782	0.297	-50.5824	0.201	-66.5557	0.048	-92.0133
0.469	-38.2082	0.377	-50.3294	0.24	-68.3794	0.036	-95.2569
Mean ± S.D.							
0.359	-49.112	0.263	-62.383	0.20675	-70.363	0.057	-91.780
0.076	8.541	0.059	8.460	0.024	4.524	0.038	5.807

Day 18		Day 21		Day 23	
area	% variat.	area	% variat.	area	% variat.
0.027	-95.3448	0	-100	0	-100
0.041	-94.696	0.027	-96.5071	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0.017	-97.7602	0	-100	0	-100
Mean ± S.D.					
0.011	-98.475	0.003	-99.563	0.000	-100.000
0.016	2.275	0.010	1.235	0.000	0.000

Table 3A: Wound healing data - Experiment 3

Component B (004-001) 1µg								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.746	0.709	-4.95979	0.584	-21.7158	0.477	-36.059	0.305	-59.1153
0.92	0.659	-28.3696	0.404	-56.087	0.304	-66.9565	0.242	-73.6957
0.687	0.618	-10.0437	0.466	-32.1689	0.444	-35.3712	0.41	-40.3202
0.818	0.822	0.488998	0.503	-38.5086	0.388	-52.5672	0.372	-54.5232
0.742	0.571	-23.0458	0.451	-39.2183	0.399	-46.2264	0.372	-49.8652
0.716	0.677	-5.44693	0.636	-11.1732	0.548	-23.4637	0.503	-29.7486
0.833	0.638	-23.4094	0.487	-41.5366	0.402	-51.7407	0.377	-54.7419
0.659	0.52	-21.0926	0.49	-25.6449	0.425	-35.5083	0.332	-49.6206
0.738	0.724	-1.89702	0.571	-22.6287	0.491	-33.4688	0.466	-36.8564
0.705	0.545	-22.695	0.233	-66.9504	0.195	-72.3404	0.152	-78.4397
Mean ± S.D.								
0.756	0.648	-14.047	0.471	-35.563	0.407	-45.370	0.353	-52.693
0.079	0.091	10.696	0.112	16.759	0.100	15.606	0.103	15.277

Day 9		Day 11		Day 14		Day 16		
area	% variat.	area	% variat.	area	% variat.	area	% variat.	
0.41	-45.0402	0.129	-82.7078	0.056	-92.4933	0	-100	
0.181	-80.3261	0.09	-90.2174	0.008	-99.1304	0	-100	
0.366	-46.7249	0.15	-78.1659	0.099	-85.5895	0	-100	
0.345	-57.824	0.198	-75.7946	0.063	-92.2983	0.033	-95.9658	
0.271	-63.4771	0.12	-83.8275	0	-100	0	-100	
0.475	-33.6592	0.267	-62.7095	0.02	-97.2067	0	-100	
0.35	-57.9832	0.204	-75.5102	0.045	-94.5978	0	-100	
0.246	-62.6707	0.11	-83.308	0.017	-97.4203	0	-100	
0.401	-45.664	0.18	-75.6098	0.031	-95.7995	0.008	-98.916	
0.11	-84.3972	0.189	-73.1915	0.008	-98.8652	0.008	-98.8652	
Mean ± S.D.								
0.316	-57.777	0.164	-78.104	0.035	-95.340	0.005	-99.375	
0.112	15.939	0.054	7.507	0.031	4.340	0.010	1.284	

Day 18		Day 21		Day 23		
area	% variat.	area	% variat.	area	% variat.	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
Mean ± S.D.						
0	-100.000	0	-100	0	-100	
0.000	0.000	0.000	0.000	0.000	0.000	

Table 3B: Wound healing data - Experiment 3

Phosphate buffer								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.785	0.75	-4.4586	0.747	-4.84076	0.285	-63.6943	0.271	-65.4777
0.673	0.768	14.1159	0.731	8.618128	0.626	-6.98366	0.612	-9.06389
0.785	0.772	14.71025	0.747	-4.84076	0.487	-37.9618	0.439	-44.0764
0.902	0.902	0	0.862	-4.43459	0.754	-16.408	0.739	-18.071
0.785	0.742	-5.47771	0.766	-2.42038	0.535	-31.8471	0.531	-32.3567
0.694	0.694	0	0.672	-3.17003	0.448	-35.4467	0.433	-37.6081
0.733	0.846	15.4161	0.743	1.364256	0.506	-30.9686	0.487	-33.5607
0.666	0.742	11.41141	0.778	16.81682	0.535	-19.6697	0.475	-28.6787
0.768	0.765	-0.39063	0.687	-10.5469	0.312	-59.375	0.322	-58.0729
Mean ± S.D.								
0.755	0.776	5.036	0.748	-0.384	0.499	-33.595	0.479	-36.330
0.074	0.062	8.698	0.055	8.301	0.145	18.710	0.141	17.828

Day 9		Day 11		Day 14		Day 16		
area	% variat.	area	% variat.	area	% variat.	area	% variat.	
0.26	-66.879	0.221	-71.8471	0.107	-86.3694	0.042	-94.6497	
0.522	-22.4368	0.217	-67.7563	0.057	-91.5305	0	-100	
0.401	-48.9172	0.374	-52.3567	0.15	-80.8917	0.096	-87.7707	
0.601	-33.3703	0.324	-64.0798	0.103	-88.5809	0.038	-95.7871	
0.535	-31.8471	0.358	-54.3949	0.15	-80.8917	0.04	-94.9045	
0.382	-44.9568	0.238	-65.7061	0.128	-81.5562	0.053	-92.3631	
0.46	-37.2442	0.3	-59.0723	0.1	-86.3574	0.058	-92.0873	
0.255	-61.7117	0.264	-60.3604	0.101	-84.8348	0.102	-84.6847	
0.297	-61.3281	0.269	-64.974	0.025	-96.7448	0	-100	
Mean ± S.D.								
0.413	-45.410	0.285	-62.283	0.102	-86.418	0.048	-93.583	
47.474	15.475	0.058	6.308	0.041	5.300	0.036	5.084	

Day 18		Day 21		Day 23		
area	% variat.	area	% variat.	area	% variat.	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0.008	-99.1131	0	-100	0	-100	
0.012	-98.4713	0.012	-98.4713	0	-100	
0.041	-94.0922	0.008	-98.8473	0	-100	
0.008	-98.9086	0	-100	0	-100	
0.092	-86.1862	0.095	-85.7357	0	-100	
0	-100	0	-100	0	-100	
Mean ± S.D.						
0.018	-97.419	0.013	-98.117	0.000	-100.000	
0.031	4.611	0.031	4.680	0.000	0.000	

Table 3C: Wound healing data - Experiment 3

Component B (004-001) 4 µg								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.826	0.604	-26.8765	0.512	-38.0145	0.293	-64.5278	0.248	-69.9758
0.731	0.635	-13.1327	0.515	-29.5486	0.371	-49.2476	0.324	-55.6772
0.785	0.659	-16.051	0.538	-31.465	0.43	-45.2229	0.358	-54.3949
0.803	0.742	-7.59651	0.601	-25.1557	0.49	-38.9788	0.427	-46.8244
0.727	0.691	-4.95186	0.676	-7.01513	0.509	-29.9862	0.468	-35.6259
0.785	0.581	-25.9873	0.506	-35.5414	0.379	-51.7197	0.278	-64.586
0.866	0.523	-39.6074	0.329	-62.0092	0.218	-74.8268	0.161	-81.4088
0.757	0.666	-12.0211	0.582	-23.1176	0.407	-46.2351	0.319	-57.86
0.799	0.526	-34.1677	0.319	-60.0751	0.236	-70.4631	0.169	-78.8486
0.81	0.568	-29.8765	0.430	-46.9136	0.374	-53.8272	0.292	-63.9506
Mean ± S.D.								
0.789	0.620	-21.027	0.501	-35.886	0.371	-52.504	0.304	-60.915
0.043	0.072	11.842	0.114	16.883	0.098	13.987	0.099	13.999

Day 9		Day 11		Day 14		Day 16	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.187	-77.3608	0.106	-87.1671	0.02	-97.5787	0	-100
0.208	-71.5458	0.132	-81.9425	0	-100	0	-100
0.223	-71.5924	0.102	-87.0064	0	-100	0	-100
0.283	-64.7572	0.126	-84.3088	0.01	-98.7547	0	-100
0.311	-57.2215	0.145	-80.055	0	-100	0	-100
0.188	-76.051	0.008	-98.9809	0	-100	0	-100
0.138	-84.0647	0.008	-99.0762	0	-100	0	-100
0.264	-65.1255	0.135	-82.1664	0.042	-94.4518	0	-100
0.173	-78.3479	0.081	-89.8623	0	-100	0	-100
0.212	-73.8272	0.082	-89.8765	0	-100	0	-100
Mean ± S.D.							
0.219	-71.989	0.093	-88.044	0.007	-99.079	0.000	-100.000
0.053	7.837	0.049	6.662	0.014	1.817	0.000	0.000

Day 18		Day 21		Day 23	
area	% variat.	area	% variat.	area	% variat.
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
Mean ± S.D.					
0	-100.000	0	-100	0	-100
0.000	0.000	0.000	0.000	0.000	0.000

Table 3D: Wound healing data - Experiment 3

Component B (004-001) 2µg								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.776	0.591	-23.8402	0.577	-25.6443	0.285	-63.6943	0.202	-74.2675
0.785	0.548	-30.1911	0.447	-43.0573	0.357	-53.9948	0.309	-60.1804
0.776	0.68	-12.3711	0.587	-24.3557	0.435	-44.0874	0.319	-58.9974
0.778	0.498	-35.990	0.194	-75.0643	0.179	-76.933	0.112	-85.567
0.776	0.428	-44.845	0.183	-76.4175	0.152	-81.071	0.092	-88.543
0.803	0.638	-20.548	0.597	-25.6538	0.427	-44.183	0.365	-52.2876
0.765	0.72	-5.882	0.657	-14.1176	0.496	-41.3018	0.357	-57.7515
0.845	0.591	-30.059	0.512	-39.4083	0.427	-47.284	0.337	-58.3951
0.81	0.669	-17.407	0.567	-30	0.518	-36.0494	0.355	-56.1728
0.834	0.631	-24.341	0.469	-43.765	0.316	-60.2416	0.233	-70.6844
Mean ± S.D.								
0.7948	0.599	-24.547	0.479	-39.748	0.359	-54.884	0.268	-66.285
0.027	0.089	11.398	0.165	21.096	0.125	15.301	0.103	12.797

Day 9		Day 11		Day 14		Day 16	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.173	-77.7062	0.063	-91.8814	0	-100	0	-100
0.229	-70.828	0.093	-88.1529	0	-100	0	-100
0.246	-68.299	0.056	-92.7835	0.007	-99.0979	0	-100
0.107	-86.2468	0	-100	0	-100	0	-100
0.008	-98.9691	0	-100	0	-100	0	-100
0.141	-82.4408	0.08	-90.0374	0	-100	0	-100
0.316	-58.6928	0.181	-76.3399	0.114	-85.098	0	-100
0.196	-76.8047	0.086	-89.8225	0	-100	0	-100
0.28	-65.4321	0.188	-76.7901	0.106	-86.9136	0.053	-93.4568
0.153	-81.1111	0.008	-99.0408	0	-100	0	-100
Mean ± S.D.							
0.185	-76.653	0.076	-90.485	0.023	-97.111	0.005	-99.346
0.090	11.531	0.067	8.532	0.046	5.875	0.017	2.069

Day 18		Day 21		Day 23	
area	% variat.	area	% variat.	area	% variat.
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
0	-100	0	-100	0	-100
Mean ± S.D.					
0.000	-100.000	0.000	-100.000	0.000	-100.000
0.000	0.000	0.000	0.000	0.000	0.000

Table 3E: Wound healing data - Experiment 3

Component B (004-001) 1mg/kg, i.v.								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.702	0.532	-24.2165	0.233	-66.8091	0.159	-77.3504	0.18	-74.359
0.713	0.545	-23.5624	0.401	-43.7588	0.321	-54.979	0.311	-56.3815
0.854	0.731	-14.4028	0.608	-28.8056	0.447	-47.6581	0.43	-49.6487
0.698	0.597	-14.470	0.421	-39.6848	0.321	-54.0115	0.297	-57.4499
0.702	0.591	-15.812	0.459	-34.6154	0.329	-53.1339	0.301	-57.1225
0.791	0.529	-33.123	0.433	-45.2592	0.329	-58.4071	0.263	-66.7509
0.799	0.611	-23.529	0.387	-51.5645	0.231	-71.0889	0.113	-85.8573
0.842	0.791	-6.057	0.462	-45.1306	0.418	-50.3563	0.352	-58.1948
0.834	0.628	-24.700	0.481	-42.3261	0.393	-52.8777	0.311	-62.7098
0.886	0.818	-7.675	0.694	-21.6704	0.55	-37.9233	0.54	-39.0519
Mean ± S.D.								
0.7821	0.637	-18.755	0.458	-41.962	0.350	-55.779	0.310	-60.753
0.072	0.106	8.482	0.125	12.373	0.110	11.255	0.119	12.906

Day 9		Day 11		Day 14		Day 16	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.106	-84.9003	0.012	-98.2906	0	-100	0	-100
0.229	-67.8822	0.088	-87.6578	0	-100	0	-100
0.324	-62.0609	0.127	-85.1288	0.007	-99.1803	0.008	-99.0632
0.204	-70.7736	0.027	-96.1318	0	-100	0	-100
0.137	-80.4843	0.043	-93.8746	0	-100	0	-100
0.137	-82.6802	0.008	-98.9886	0	-100	0	-100
0.053	-93.3667	0	-100	0	-100	0	-100
0.307	-63.5392	0.138	-83.6105	0.011	-98.6936	0	-100
0.2	-76.0192	0.072	-91.3669	0	-100	0	-100
0.39	-55.9819	0.212	-76.0722	0.013	-98.5327	0	-100
Mean ± S.D.							
0.209	-73.769	0.073	-91.112	0.003	-99.641	0.001	-99.906
0.106	11.734	0.069	7.858	0.005	0.600	0.003	0.296

Day 18		Day 21		Day 23		
area	% variat.	area	% variat.	area	% variat.	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
0	-100	0	-100	0	-100	
Mean ± S.D.						
0.000	-100.000	0.000	-100.000	0.000	-100.000	
0.000	0.000	0.000	0.000	0.000	0.000	

BNSDOCID: <WO___9739765A1_I_>

Table 4A: Wound healing data - Experiment 4

Phosphate buffer								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.813	0.817	0.492005	0.785	-3.44403	0.393	-51.6605	0.297	-63.4686
0.813	0.809	-0.492	0.817	0.492005	0.462	-43.1734	0.541	-33.4563
0.954	0.981	2.830189	0.912	-4.40252	0.672	-29.5597	0.584	-38.7841
0.833	0.821	-1.441	0.716	-14.0456	0.48	-42.377	0.404	-51.5006
0.841	0.882	4.875	0.878	4.399524	0.758	-9.8692	0.694	-17.4792
0.813	0.805	-0.984	0.608	-25.2153	0.407	-49.9385	0.393	-51.6605
0.805	0.821	1.988	0.746	-7.32919	0.544	-32.4224	0.444	-44.8447
0.769	0.825	7.282	0.762	-0.91027	0.69	-10.2731	0.657	-14.5644
0.845	0.874	3.432	0.845	0	0.639	-24.3787	0.636	-24.7337
0.817	0.829	1.469	0.789	-3.42717	0.496	-39.2901	0.387	-52.6316
Mean ± S.D.								
0.830	0.846	1.945	0.786	-5.388	0.554	-33.294	0.504	-39.312
0.8303	0.054	2.757	0.087	8.563	0.127	14.919	0.136	16.428

Day 9		Day 11		Day 14		Day 16	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.269	-66.9127	0.173	-78.7208	0.125	-84.6248	0.091	-88.8069
0.3	-63.0996	0.19	-76.6298	0.182	-77.6138	0.062	-92.3739
0.481	-49.5807	0.407	-57.3375	0.365	-61.74	0.227	-76.2055
0.345	-58.5834	0.264	-68.3073	0.239	-71.3085	0.112	-86.5546
0.522	-37.931	0.271	-67.7765	0.173	-79.4293	0.137	-83.7099
0.283	-65.1907	0.289	-64.4526	0.168	-79.3358	0.124	-84.7478
0.361	-55.1553	0.285	-64.5963	0.214	-73.4161	0.074	-90.8075
0.472	-38.6216	0.311	-59.5579	0.271	-64.7594	0.155	-79.844
0.374	-55.7396	0.352	-58.3432	0.264	-68.7574	0.148	-82.4852
0.246	-69.8898	0.261	-68.0539	0.19	-76.7442	0.112	-86.2913
Mean ± S.D.							
0.365	-56.070	0.280	-66.378	0.219	-73.773	0.124	-85.183
0.097	11.175	0.069	7.193	0.069	7.162	0.047	4.925

Day 18		Day 21		Day 23		
area	% variat.	area	% variat.	area	% variat.	
0.071	-91.2669	0.009	-98.893	0	-100	
0.044	-94.5879	0	-100	0	-100	
0.099	-89.6226	0.27	-71.6981	0	-100	
0.072	-91.3565	0	-100	0	-100	
0.092	-89.0606	0.031	-96.3139	0	-100	
0.069	-91.5129	0	-100	0	-100	
0.043	-94.6584	0	-100	0	-100	
0.031	-95.9688	0.28	-63.5891	0	-100	
0.047	-94.4379	0	-100	0	-100	
0.066	-91.9217	0.008	-99.0208	0	-100	
Mean ± S.D.						
0.063	-92.439	0.060	-92.951	0.000	-100.000	
0.022	2.334	0.114	13.522	0.000	0.000	

Table 4B: Wound healing data - Experiment 4

Bovine Serum Albumin								
Day 0	Day 1		Day 3		Day 5		Day 7	
area	area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.785	0.821	4.585987	0.805	2.547771	0.765	-2.54777	0.622	-20.7643
0.857	0.858	0.116686	0.786	-8.28471	0.65	-24.154	0.625	-27.0712
0.837	0.874	4.42055	0.825	-1.43369	0.746	-10.8722	0.544	-35.006
0.781	0.817	4.609475	0.794	1.664533	0.708	-9.34699	0.611	-21.767
0.853	0.924	8.323564	0.882	3.399766	0.735	-13.8335	0.668	-21.6882
0.845	0.895	5.91716	0.785	-7.10059	0.727	-13.9645	0.618	-26.8639
0.833	0.893	7.202881	0.878	5.402161	0.675	-18.9676	0.453	-45.6182
0.854	0.916	7.259953	0.899	5.269321	0.712	-16.6276	0.48	-43.7939
Mean ± S.D.								
0.831	0.875	5.305	0.832	0.183	0.715	-13.789	0.578	-30.322
0.031	0.040	2.553	0.047	5.327	0.038	6.513	0.077	9.993

Day 9		Day 11		Day 14		Day 16	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.538	-31.465	0.344	-56.1783	0.244	-68.9172	0.169	-78.4713
0.557	-35.0058	0.368	-57.0595	0.329	-61.6103	0.162	-81.0968
0.413	-50.6571	0.287	-65.7109	0.226	-72.9988	0.101	-87.9331
0.554	-29.0653	0.329	-57.8745	0.259	-66.8374	0.138	-82.3303
0.448	-47.4795	0.352	-58.7339	0.239	-71.9812	0.173	-79.7186
0.561	-33.6095	0.299	-64.6154	0.255	-69.8225	0.21	-75.1479
0.314	-62.3049	0.255	-69.3878	0.22	-73.5894	0.166	-80.072
0.404	-52.6932	0.266	-68.8525	0.239	-72.0141	0.166	-80.5621
Mean ± S.D.							
0.474	-42.785	0.313	-62.302	0.251	-69.721	0.161	-80.667
0.092	12.097	0.042	5.443	0.034	3.979	0.031	3.631

Day 18		Day 21		Day 23		Day 25	
area	% variat.	area	% variat.	area	% variat.	area	% variat.
0.062	-92.1019	0.007	-99.1083	0	-100	0	-100
0.039	-95.4492	0.021	-97.5496	0	-100	0	-100
0	-100	0.000	-100	0	-100	0	-100
0.081	-89.6287	0.031	-96.0307	0	-100	0	-100
0.094	-88.9801	0.055	-93.5522	0.018	-97.8898	0	-100
0.145	-82.8402	0	-100	0	-100	0	-100
0.083	-90.036	0.008	-99.0396	0	-100	0	-100
0.107	-87.4707	0	-100	0	-100	0	-100
Mean ± S.D.							
0.076	-90.813	0.015	-98.160	0.002	-99.736	0.000	-100.000
0.044	5.178	0.020	2.329	0.006	0.746	0.000	0.000

CLAIMS

1. Use of Component B for the manufacture of a medicament useful as cicatrizant.

2. The use according to claim 1 in the treatment of wounds, ulcers and other traumatic lesions to any of the tissues in the body.

3. A pharmaceutical composition useful as cicatrizant comprising Component B, as active ingredient, together with a pharmaceutically acceptable excipient.

4. Method of treatment of wounds, ulcers and other traumatic lesions to any of the tissues in the body, comprising administering an effective amount of Component B, together with a pharmaceutically acceptable carrier.

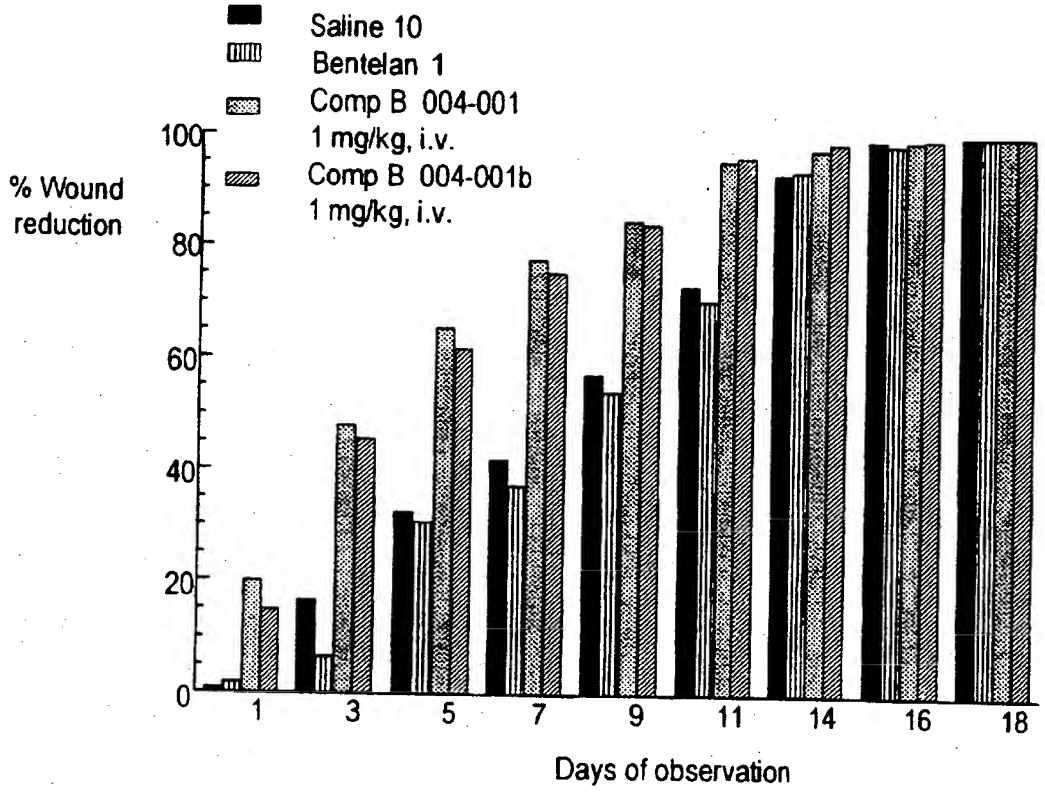

Figure 1

BNSDOCID: <WO___9739765A1_I_>

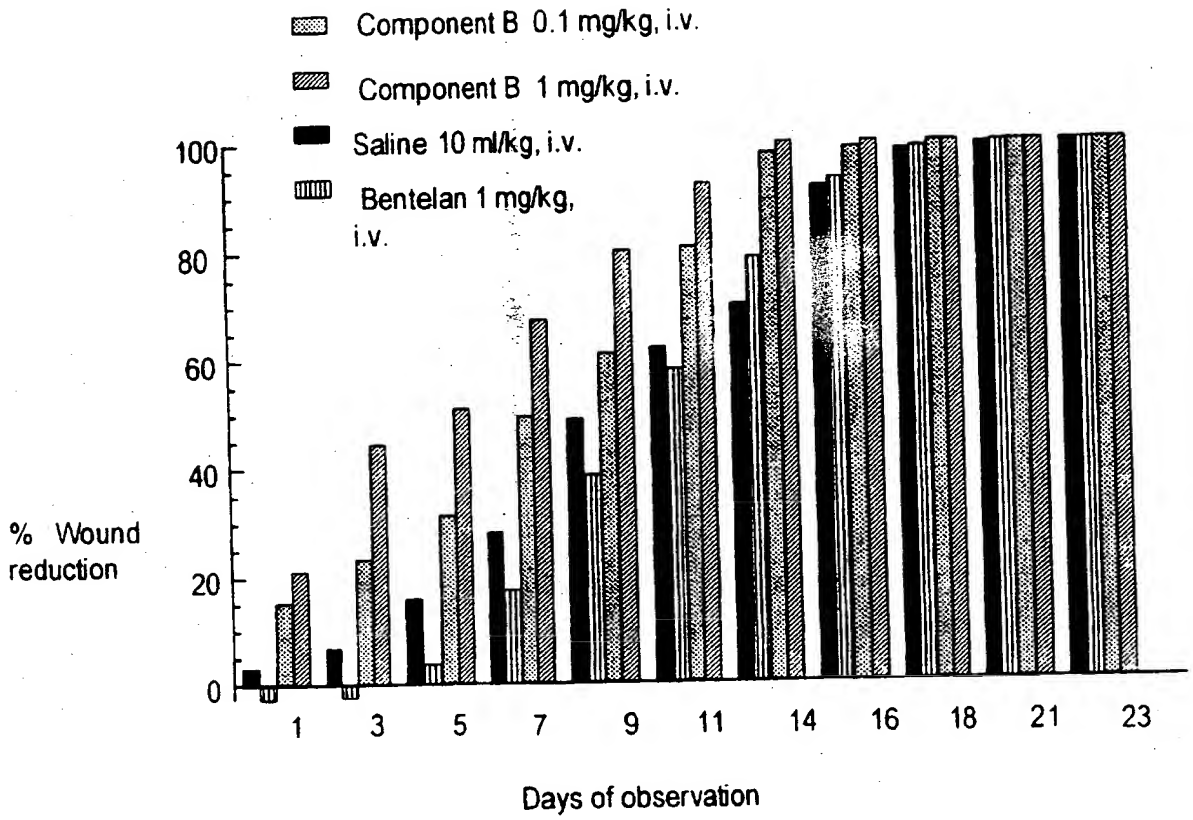
Component B 0.1 mg/kg, i.v.
Component B 1 mg/kg, i.v.
Saline 10 ml/kg, i.v.
Bentelan 1 mg/kg, i.v.
% Wound reduction
100
80
60
40
20
0
1
3
5
7
9
11
14
16
18
21
23
Days of observation

Figure 2

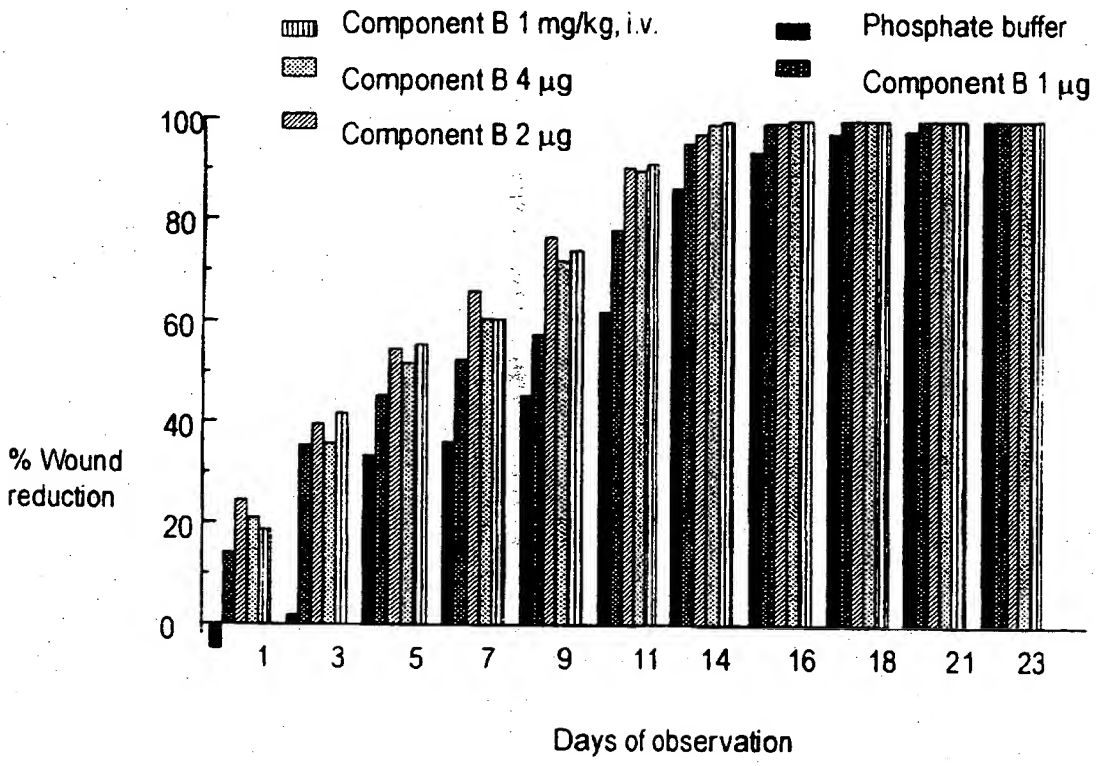
Component B 1 mg/kg, i.v.
Component B 4 µg
Component B 2 µg
Phosphate buffer
Component B 1 µg
% Wound reduction
100
80
60
40
20
0
1
3
5
7
9
11
14
16
18
21
23
Days of observation

Figure 3

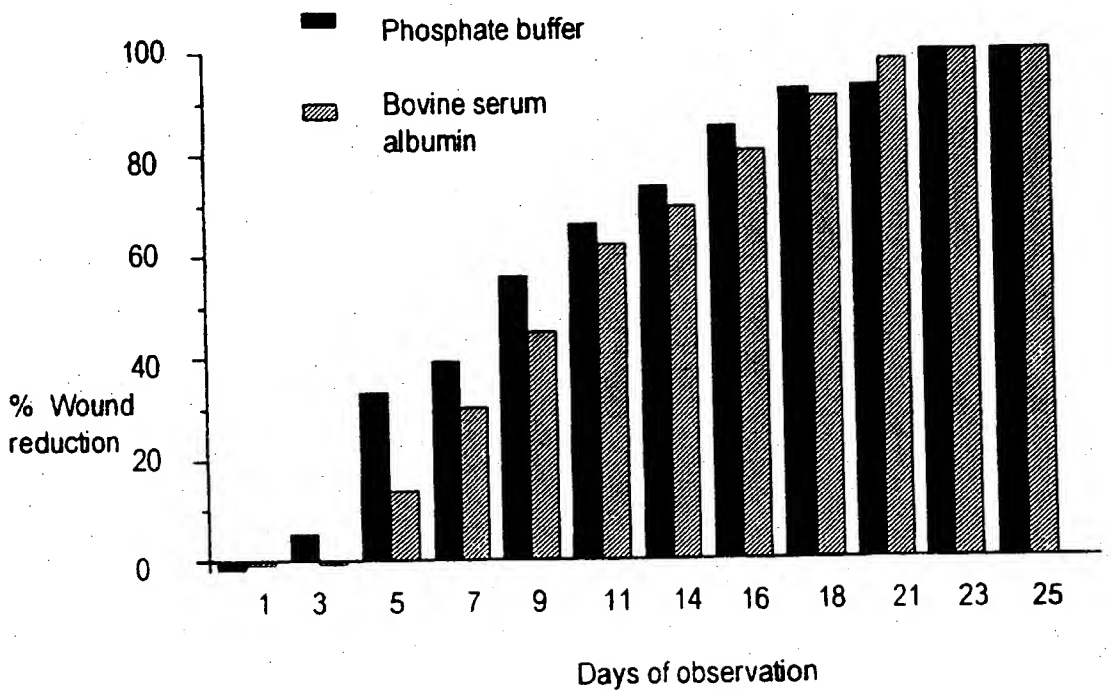
Phosphate buffer
Bovine serum albumin
100
80
60
40
20
0
% Wound reduction
1
3
5
7
9
11
14
16
18
21
23
25
Days of observation

Figure 4

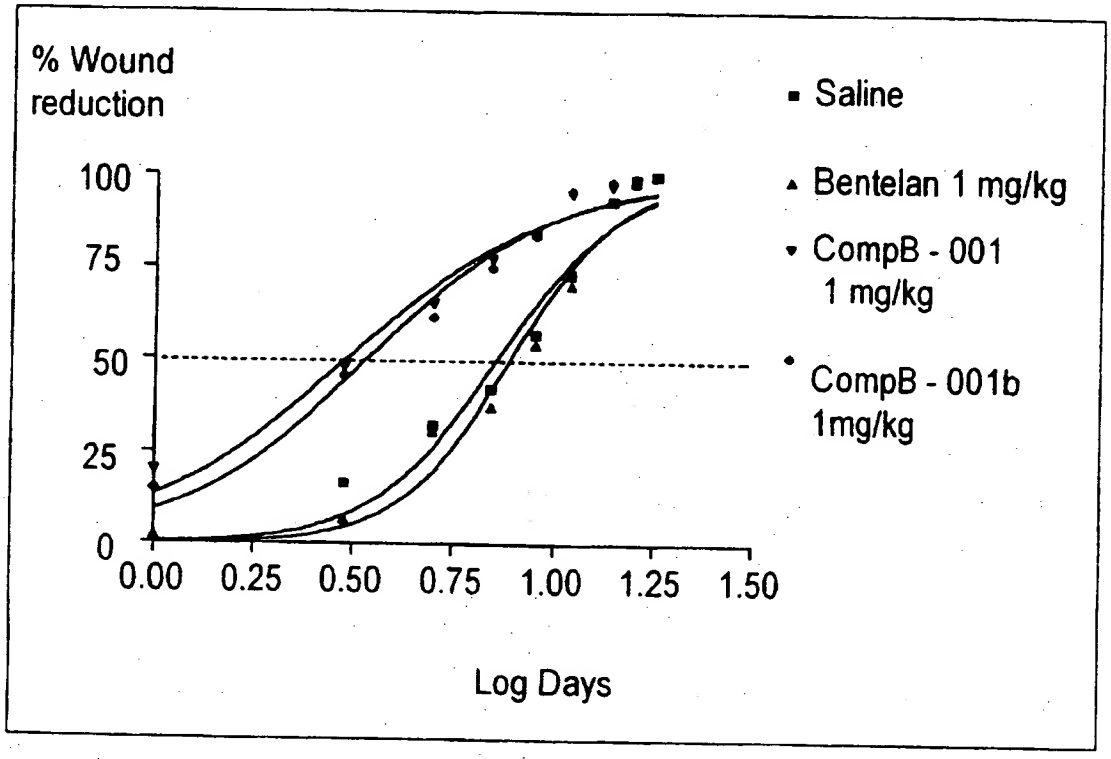

Figure 5

BNSDOCID: <WO___9739765A1_I_>

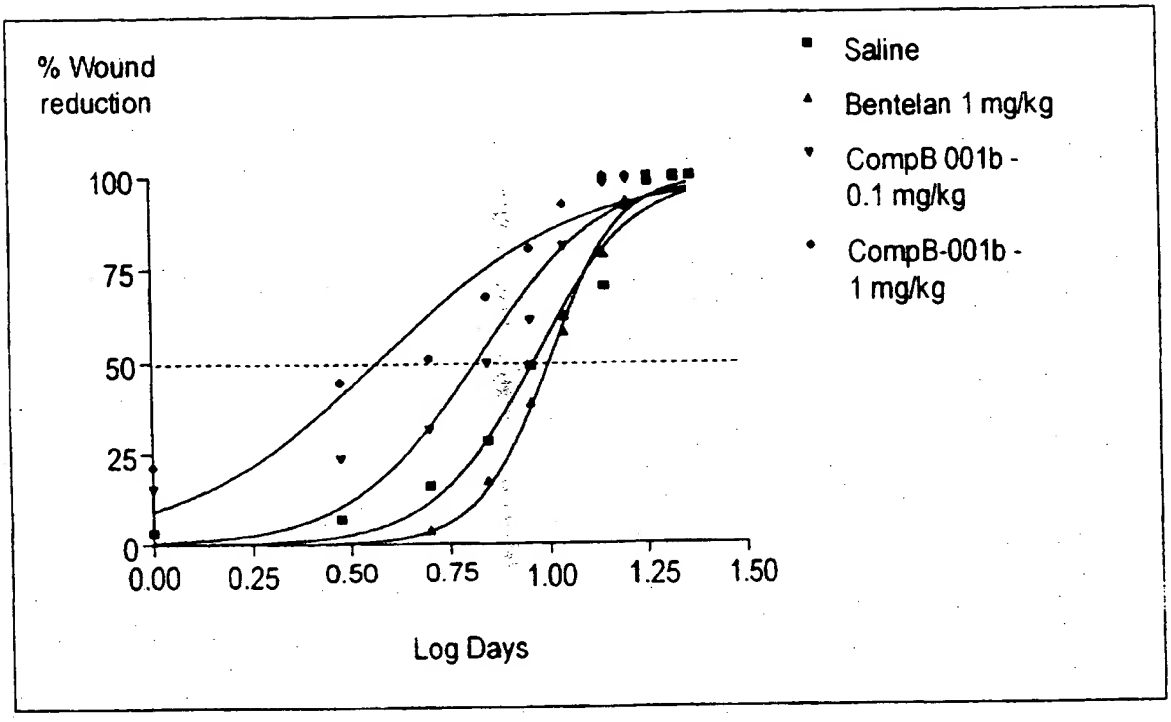
% Wound reduction
100
75
50
25
0
0.00
0.25
0.50
0.75
1.00
1.25
1.50
Log Days
Saline
Bentelan 1 mg/kg
CompB 001b - 0.1 mg/kg
CompB-001b - 1 mg/kg

Figure 6

Wound area

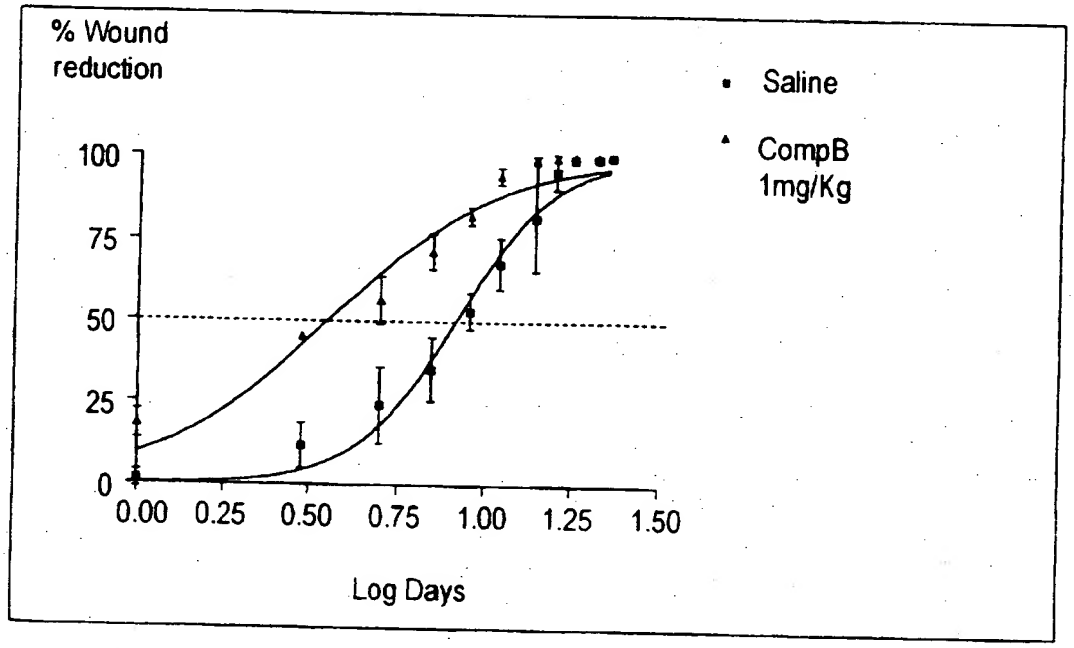

Figure 7

BNSDOCID: <WO___9739765A1_I_>

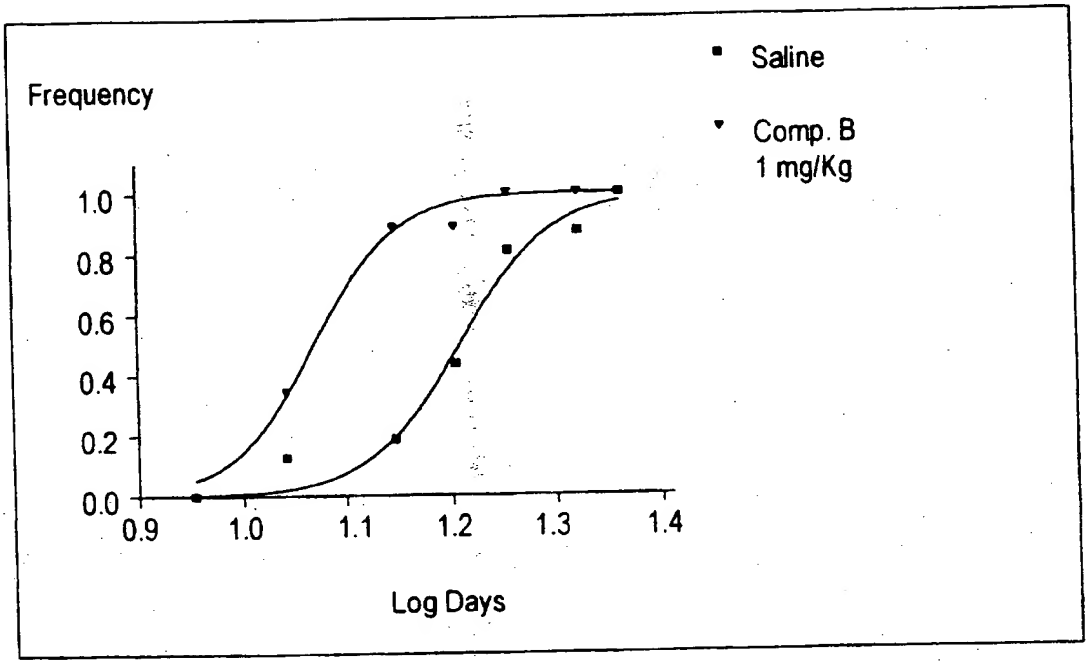
Cumulative Frequency
Frequency
Saline
Comp. B
1 mg/Kg
1.0
0.8
0.6
0.4
0.2
0.0
0.9
1.0
1.1
1.2
1.3
1.4
Log Days

Figure 8

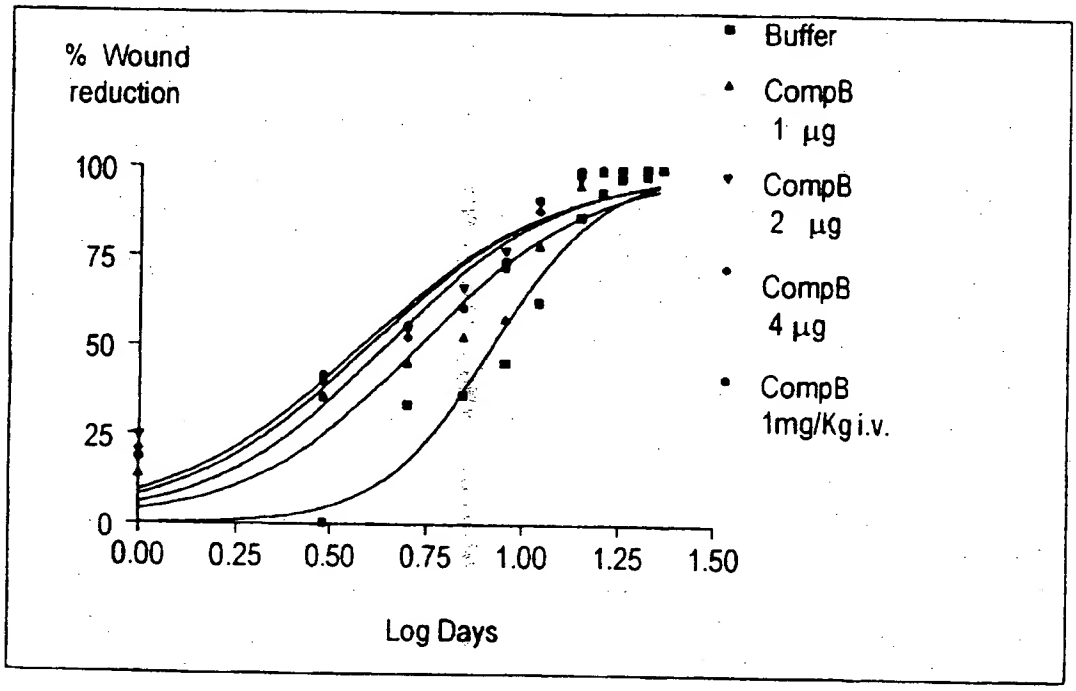

Figure 9

BNSDOCID: <WO___9739765A1_I_>

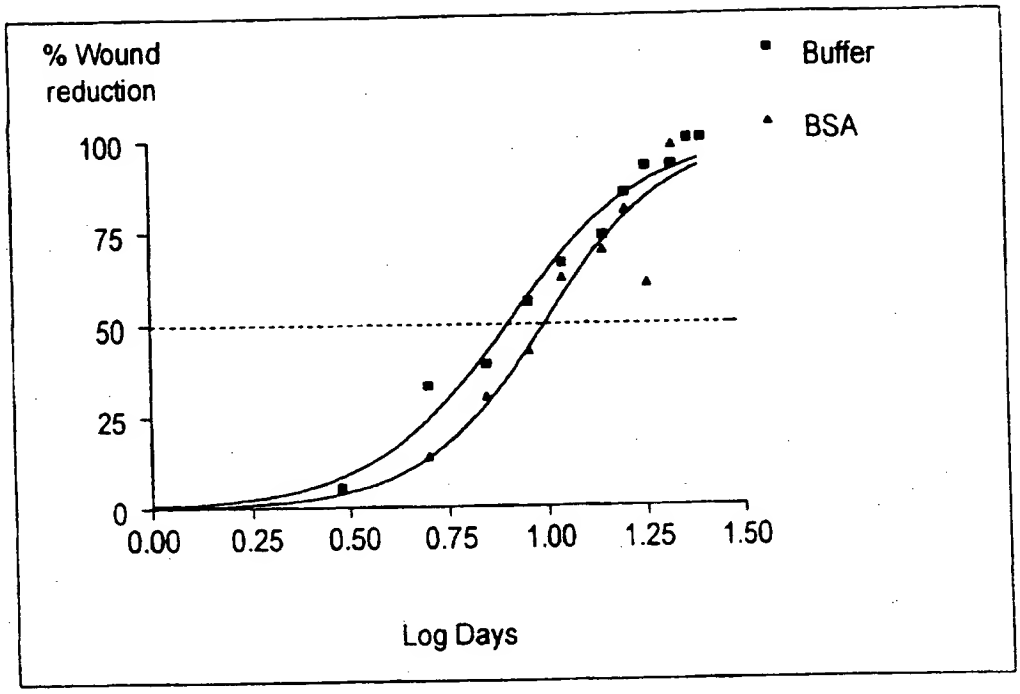
% Wound reduction
Buffer
BSA
100
75
50
25
0
0.00
0.25
0.50
0.75
1.00
1.25
1.50
Log Days

Figure 10

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PC I/EP 96/01702

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 14959 (APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.) 7 July 1994 cited in the application see page 13, line 5 - page 14, line 1; claims 1,12-16 ---	1-4
A	EP,A,0 046 039 (G.D. SEARLE & CO.) 17 February 1982 see page 1, line 8 - line 16 see page 13, line 13 - line 23 -----	1-4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 1996	18.12.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Ryckebosch, A

Form PCT ISA/210 (second sheet) (July 1992)

BNSDOCID: <WO___9739765A1_I_>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/01702

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 4 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort jusufying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/01702

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9414959	07-07-94	IT-B-	1257184	10-01-96
		AU-A-	5833594	19-07-94
		EP-A-	0675956	11-10-95
		FI-A-	953091	21-06-95
		JP-T-	8509359	08-10-96
		NO-A-	952494	21-08-95
		ZA-A-	9309621	22-06-95
EP-A-46039	17-02-82	AU-B-	547077	03-10-85
		AU-A-	7364581	11-02-82
		CA-A-	1197797	10-12-85
		JP-A-	57122096	29-07-82
		US-A-	4719180	12-01-88

BNSDOCID: <WO___9739765A1_I_>